SOME BIOCHEMICAL AND PHYSIOLOGICAL CORRELATIONS DEVELOPED FROM CLINICAL OBSERVATIONS WITH VARIOUS TOXIC MUSHROOMS AND MEDICINAL PRODUCTS

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Perhaps, first, I should establish a rationale for having a neuropsychiatrist on the program of industrial microbiologists. Individuals in your category must focus a sharp scientific eye on very small things, and the other eye might be focused on the idea of practical application. In fact, initially, it may take the fullest or complete focus of your attention to a small biological sphere or area before the mind's eye turns to classify the observation into its correct place in the larger biological scheme. Contemporary psychiatry would do well to (or must) pass through a similar 'micro' orientation regarding the fundaments of its material.

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Terminology is always important in science. The term psychiatry is misleading. It implies an emphasis on psyche or mind. But the mind in the neurological or physiological sense is only another variant in the fundamental functioning of a neural system. True the mind has a special significance or importance in that its specific content is coded into the human individual as its life period progresses. But for the psychiatrist to place a main emphasis on the quality and quantity of the mind-content makes him only a competitor with the social scientist, the educator, the psychologist, the clergyman, the sociologist. To presume that the properties of the organic and physiological substrate of the mind in the nervous system are always constant is to overlook the more significant feature of potential instability in the entire sequence in the complex of mind functioning. Grundfest in "Evolution Of Conduction" states, "The rapidly expanding organizational and functional complexities of the nervous system arising from mere increase in their number accompany and in turn make possible the expanding capacities of animals in different evolutionary stages to cope with their environment. One may hope optimistically that Homo sapiens of future generations will be endowed with a more highly developed and better functioning nervous system than are his current progenitors". To most of you who are not active in my field of work I may not have the problem with psychiatric preconception. I hope that I made my point clear that in psychiatry an emphasis of observation is needed to man's internal environment, i.e., the mind's organic and psysiological substrate, how these latter integrate with the fundamental functions of the nervous system and in turn the functional interdependence of the nervous system with other systems of the body, most significantly with the metabolic.

Now, I should like to approach my observations of mushrooms with the following clinical analogy. If a drop of dilute atropine is placed in the conjunctival sac, the pupil of the eye dilates within a few minutes. Here is a situation in clinical practice where the opthalmalogist produces a relatively local effect with one specific chemical, hopefully, upon one or a specific nerve which anatomically is so located as to make this technique feasible. I said, "hopefully upon the one nerve" because the atropine is also absorbed into the local tissue fluids from whence it enters the systemic circulation. Because even the few drops needed to dilate the

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pupils and even when applied to a serous membrane type of tissue rather than the usual routes of medicinal administration, produce in some undesirable systemic effects (palpitation, dry mouth, disturbed intestinal activity), the diluted atropine is being replaced by even more dilute products capable of dilating the pupil but not as active upon other tissues if absorbed systemically. Please, note how many observations can be derived from or how many variables must be considered in this one situation most of which are pertinent to the clinical study of all neurophysiologically significant pharmacological materials. Among these variables of consistent consequence are the factors of dosage, avenues of absorption, local effects, systemic effects, undesirable side-effects, time required for induction of effects, and the variability of response of the individual human. In psychiatry, in addition, the subjective feeling tone arising in a complex situation, such as having some "burning" drops placed in the eyes at a doctor's office by personnel of variable attitudes, is of consequence in the measurement of drug effects since the subject's stressor mechanism may become activated in the situation to produce complicating effects from the sympathetic-autonomic apparatus. Perhaps in some instances the tension-reaction, that is the anxiety, is so great that the atropine is almost unnecessary to dilate the pupils. An additional item within the feature of control in this type of clinical test observation is the observer's ability to be objective, and here again semantically correct in his reporting. Returning to the subject with his pupils now dilated, one could describe him as "wide-eyed" or "wild eyed". The former expression intends to describe the status of the pupils only, whereas, the latter implies in addition an observation as to the affective, attitudonal or mental state of the subject. From this former example of a specific fairly well known chemical applied by a specific route, if one keeps in mind some of the tangible and seemingly intangible variables to be measured, let us turn and compare it to a situation where a human individual has taken a bite of food, let us say meat or perhaps mushroom. Now we have a condition where a number of specific chemicals or prechemicals are brought into the organism by another even natural route. The variables to be considered may not be more numerous but each variable becomes more complex inasmuch as the time factor in securing effects depends upon almost the entire complex of metabolsim in general, upon the special process of some particular chemical, the additional complication of the interaction between the metabolites formed from the bite of food, and interaction between the newly processed metabolites present with those in the body's pool of such substances. Fortunately, much is known about the metabolic process. Perhaps most of it was learned from the usually species-fixed metabolism of the subhuman animal, but much of it applies to man. Whether this is also true regarding the human nervous system is controversial. In my opinion, in this most important area, namely, the controlling effects of and the needs of the nervous system, that is, the neurally affected metabolism in man contains either primary or potential significant differences and/or variations of pathways from those of the infra-human form. The latter may become so extreme at times that they might be considered under the term errors of metabolism or metabolic errors.

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All of the preceding has been presented in the hope that it will serve as a background to my discussion of mushrooms. Actually, my statements here are not so far removed to that of mainly trying to find a method to study and to understand the effects of some mushrooms as observed in the human. There is an extensive literature rapidly accumulating on the history of the mushroom's place in medicinal practices. This history dates as far back as there are intelligible records. Some of the reports and claims that have been expressed as to the effects of mushrooms on man's mind and/or behavior are so unusual that they appear imaginative. This is a topic of its own and I don't have time for it here. Besides, my own interest in neuropharmacological mushroom effects did not arise from an outside source of stimulation but mainly by chance in 1949 when I personally became involved in an unusual experience that occurred after a meal which included apparently cultured mushrooms. A subsequent study of the literature verified my inference that the phenomenon which I had experienced and observed was most probably precipitated by the mushrooms in that particular meal. But I didn't come here to tell you of the concepts or speculations I had developed about mushrooms from that experience. Having had formal graduate study in medicine, I continued to apply the scientific method in my medical practice. Following the above experience, I gradually shifted my research to the investigation of mushrooms. This is clinical research of the human which probably involves the most complex complexes of neuroid substance and of metabolism. I said, "gradually I shifted my research" because prior to approximately 1952, it would have been considered irrational or complete heresy to imply that symptomatic adjustments in psychiatric material could be secured even by standard drug or chemicals. So prior to that time, to have made any favorable psychiatric claims for toxic mushrooms might have cost one his membership in organized psychiatry if not even his medical license.

Through a sequence of corresponsence and personal contacts which started late in 1951 with Dr. A.H. Smith of Michigan, I met Dr. Rolf Singer in 1953 at the Chicago Museum of Natural History. Dr. Singer verified my inferences as to the neuropharmacological effects of mushrooms, particularly the genus, Panaeolus. Nevertheless, it took several years before I was able to develop an organization to sponsor such a study. In 1955 our group became active and soon thereafter, I discovered that another group consisting of the two Wassons and Dr. Roger Heim, the mycologist, were also investigating similar effects of mushrooms among the Mexicans which situation had come to their attention as the lately deceased Mrs. Wasson, a physician, was pursuing her avocational interest in mushrooms.

My group made contact with Dr. Ralph Kneebone, who as you may know, does research in the growing of mushrooms right here at Penn State University. Upon consulting with Drs. Smith and Singer again in 1957 it was decided to explore the Panaeolus venenosus species since this mushroom was the most likely contaminant of the cultured variety. It was known to have caused unusual central nervous system effects in instances where it was accidently ingested. Happily, Dr. Kneebone succeeded in growing a sizeable amount of Panaeolus venenosus in his first try. Dr. Singer was despatched to Mexico to secure the significant mushrooms there which were intended to be used comparatively to our studies of Panaeolus. In addition, Drs. Kneebone

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and Singer were able to grow the Mexican varieties of the genus, Psilocybe, here at Penn State so that we were assured of a constant and sufficient supply of this material.

I am prepared to report in part three separate items of observation derived from the use of our mushroom material. The first item is one already to be found in the literature and consists of my taking approximately 5 grams of oven dried Psilocybe cubensis, fried in butter. For whatever it may be worth scientifically, a tendency has developed in the neurotropic-drug-investigations, for the investigator to sample his own soup, so to speak. I had already tried various amounts of Psilocybe material before. In my adventure with cubensis on a particular Sunday in December 1957, I was seeking to determine whether a comparable effect would or could be produced to the one I had experienced in 1949, the one which came my way serendipitously. First, I want to report that essential theme of my cubensis experience is one in which I was as close to feeling dead as I ever want to be, but actually for a period of nearly six hours I felt sicker than at any time in my life. Unfortunately, very few objective measurements could be made on myself since I was completely unprepared for what had evolved and transpired. I can tell you that unhappily for myself, my mind remained clear, but I believe that whatever hallucinating or disorganization of mind that is alleged to occur as a result of the Psilocybe substance was taking place in all other parts of my nervous system and other tissues. My skin was so anesthetized that I was unable to feel my own pulse. Literally, it appeared as if both the sympathetic and parasympathetic parts of my autonomic apparatus were doing battle at various times. Presumably, the sympathetic component emerged victor, if the saucer-like size of my pupils were to be used as a main criterion. I believe I have personally tested every drug that has been deposited in my office by the pharmaceutical's salesman. But for certain, I have tested some of those being used in neuropsychiatric investigation such as mescaline and lysergic acid diethylamide, which are other so-called hallucinogens. Here I experienced the standard effects I had observed or had been reported by others. In view of my cubensis observations, I proceeded cautiously or more judiciously in the experimental application of our whole mushroom material. The dried products were granulated and weighed in ½ gram amounts. I decided on this dosage-size on the basis of weighing such an amount of whole, dried, Mexican mushrooms as was reported to produce a pharmacological effect among the natives in Mexico. Of the three items to be described here, in contrast to the first, namely, my cubensis experience with its relatively random approach, the following two which are separate case studies might be viewed as systematized, if they are considered in the perspective of clinical psychiatric practices.

The first of these cases might be summarized as follows:
My patient, J.H., age 27, had been under my care since April 13, 1958. Because of homosexual thoughts, rapid pulse (112), and a moderate hypertension (165/90), he was on the following medication (May 20) designed to control his symptons:

Reserpine - conc. sol., 16 drops qid
Iproniazid - 25 mg. tablet, ½ tablet bid
Amphetamine - 5 mg. tablet, ½ tablet
Amytal - grain ½, 1 bid

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On May 4, the subject had reported a clearing of his homosexual thoughts; and by May 6, he could not restore these thoughts even if he tried. On May 6th his clinical readings were: blood pressure 120/70, pulse 72, and weight 126. The Draw-A-Person test* was used almost daily to validate his subjective claims. Although homosexual thoughts were inactivated, the positive heterosexual thoughts were asserting themselves only slightly. The subject was from Ireland via Canada, and his visa time was becoming short. He had read of my work with mushrooms, and had originally come to Chicago in the hope that mushroom effects would help. He volunteered spontaneously to try the crude material in hope of expediting the effect he was seeking. On May 20, while still on the medication listed, ½ gram P. venenosus was given without significant effect. At intervals of 2 or 3 days more experiments were attempted. One gram produced positive results. One and one-half grams produced strong favorable effects. Psilocybe caerulescens, one and one-half grams, was also tried, but a different, relatively hallucinogenic, and much less pleasant effect was secured or reported. The panaeolus venenosus effect was only minimally hallucinogenic and only in the one and one-half gram portions. There was no doubt from these observations that the Panaeolus venenosus contained psychoneurophysiologic ingredient. Its effect was clearly different than the Psilocybe. Its effect was mainly stimulatory (euphoriant) and no undesirable side effects were reported or noted. The subject asked for more of the effect which was secured with one and one-half grams of the Panaeolus.

I have rushed through the findings in this latter case since I believe the material of the succeeding study not only is more extensive but the subject was a non-patient and his findings were not complicated by any pre-medication. In fact, the subject to whom I now refer is Assistant Professor Gerhard Closs of the University of Chicago who is collaborating in our research activity and who offered to be the figureative "guinea pig" since he wanted to experience personally the effects of the chemicals he is seeking to isolate and identify. I had invited him to come to this meeting as a discussant to give you personally his various observations and inferences, but unfortunately he had earlier plans to be on the West Coast at this time.

As these case studies proceed, I have been making the following measurements:

a. Weight of subject
b. Oral temperature at variable intervals
c. Pulse, blood pressure, and sweat reactions at 10 to 15 minute intervals
d. Estimated pupillary size and reflexes at frequent intervals
e. Patient's subjective feeling-tone statement is sought (almost as often as the pulse reading)
f. My observation of the subject's reaction is continuous since I never leave the subject after he partakes of the mushrooms until the evidence indicates that the experimental process has stopped.

*Slide no. 1 and no. 2

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Before I give you a summary of my findings in this case study, I might present a few charts taken at significant points of these experiments. The time will not permit covering all the steps of even one experiment since the observations cover from 2 to 5 hour periods. However, some of this material has been in press since March, and I hope that the journal will be publishing it soon.

My summary of the findings to the present time reads as follows:

There were noticeable similarities and differences in the effects of Panaeolus venenosus and Psilocybe caerulescens which appeared to have no correlation with the quantity of raw mushroom ingested.

In the experiments conducted so far, the subjective and objective effects developed within about the same time interval after ingestion, 25 to 30 minutes, with one exception. Namely, yawning, which was observed here and elsewhere only as occurring with the Psilocybe material, usually within 5 to 10 minutes, and it proceeds until other symptoms and signs present themselves.

Reported symptoms or subjective effects which occurred with Panaeolus only or mainly were (a) a mild or moderate relaxing (tranquil) type of inebriation, (b) disturbed equilibrium, (c) either diminished motivation or blocking in the psychic (thought) process, and (d) paresthesias.

Features which obtained with Psilocybe only or mainly were (a) the aforementioned yawning in the induction period, (b) "burning" sensation in the esophageal and stomach areas, (c) a feeling of extreme tiredness, and (d) a feeling-tone of anxiety bordering on collapse associated with a sense of strong intoxication.

The factors occurring in common were (a) the extreme reduction in the pulse rate, slightly more with Psilocybe, (b) the steadiness of the systolic and diastolic components of the blood pressure with both varieties of mushrooms, except for a very brief period of drop in both diastole and systole with both Panaeolus and Psilocybe during the period of strong intoxication, (c) dilatation of the pupils (d) a drop in body temperature, seemingly more marked with Panaeolus, but productive of much more subjective effect (feeling of cold) during the period of Psilocybe intoxication and (e) sweating.

With Panaeolus there was a general drop in the total personality integration, but the internal sensation was one of feeling pleasant and relaxed; whereas, with Psilocybe there was actually disorganization associated with the feeling of panic and disagreeable intoxication.

A most significant feature is that Dr. Closs at no time perceived or reported effects that could be categorized as hallucinatory. However, in my first subject a quasi-hallucinosis developed but more with the thought processes rather than with colors. In my own cubensis experience, I had observed strange color effects and disturbed stereognosis.

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My formulation as to the meaning of these observations reads as follows: Obviously, it is unwise and perhaps unnecessary to try to correlate clinical observations where unknown chemicals or chemical complexes are ingested in combination.

But since I have had a considerable experience with psycho-neuropharmacological (psychoneurotropic) material and also with the literature of biochemistry, I offer the following tentative opinion. The relaxing subjective effects, the hypothermia, and diminished pulse found with Panaeolus resembles the effects attributed to serotonin. But the inebriation and the pupillary mydriasis probably cannot be explained as effects of serotonin.

Some of the effects observed here (and elsewhere) with Psilocybe are probably due to the serotonin-related-psilocybin already isolated from the Psilocybe mexicana (Heim) which substance probably also obtains in the Psilocybe caerulescens, the species used in our experiments. Again however, it seems unlikely that Psilocybin itself will be found to have caused the signs of mydriasis and of cerebral or cortical intoxication. Where might one turn for some reasonable explanation to this variety of effects? Is there an orienting concept that one might develop to serve as a guide to the present information and to what may evolve? Our Panaeolus mushroom as yet has not been chemically analyzed. I have Dr. Closs's paper chromatographic spread to show. (Slide no. 3)

I shall not attempt to interpret his findings but will read his summarizing paragraph of our combined paper which is in press:

"The extracts of P. venenosus, P. sphinctrinus, Psil. mexicana, Psil. cubensis, and Psil. caerulescens have been compared by paper chromatography. It was found that neither Panaeoli contain psilocybin, the main constituent of the three Psilocybe species. The extract from P. venenosus has been chromatographed, and two of the three major constituents were purified and obtained crystalline. One of these compounds could be shown to possess the same chromophore as psilocybin, a 4-oxygenated indole system, and seems most likely to be the active compound of the mushroom".

Since our material has not been isolated and identified in a final chemical way, I shall proceed with my tentative formulation of trying to explain clinical results by turning to the known chemical structure of Psilocybin (slide no. 4) which you will see when hydrolyzed yields 4-OH-Tryptamine instead of 5-OH-Tryptamine which is serotonin. Before proceeding further, I should like to bring to your attention some chemical and clinical observations with tryptophan. I have reference to the L-form of this substance, which is active in human metabolism, and which I am using clinically in a variety of combinations with B vitamins to good advantage. Tryptophan is an essential amino acid which may be derived from the metabolism of a variety of animal and vegetable proteins eaten by man. Allegedly, the metabolism of L-tryptophan yields the following (slide):

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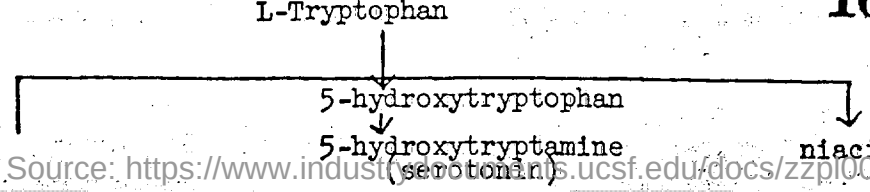

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Here we have serotonin (5-hydroxytryptamine) which chemically is closely related to 4-hydroxytryptamine. The quieting effects derived from serotonin which result seemingly from its stimulation of the parasympathetic-autonomic system have been extensively studied, and essentially consist clinically of lowered temperature, narrowed pupils, diminished pulse rate, decreased blood pressure, and subjectively less tension or anxiety. This is actually the opposite clinical picture to euphoria. However, when one turns to the other prominent metabolite of L-tryptophan, namely, niacin or nicotinic acid, entirely different inferences might be drawn (slide no. 5). A considerable literature exists to inform you that a deficiency of this substance or its precursor tryptophan as has occurred in large populations on this planet has been the basis for wide-spread pellagra, a condition characterized by mental changes, such as, anxiety, hallucinations, depression, and disorientation. In my clinical observations with niacin, either as it might be derived in exaggerated amounts from the L-tryptophan or where applied in its isolated state, a variety of results occur which suggest that many tissues are affected by the niacin; but often among these findings are those of improved energy coefficient and mood modified upwards to the level of almost mania in some. It is my impression that the niacin factor has a huge enterprise in the body. Whether its excitatory effect is accomplished through its known action in the Krebs cycle, or whether as an amine oxidase inhibitor, I am not certain. However, I am more impressed with its alleged role in the formation of diphosphopyridine nucleotide (DPN) and triphosphopyridine nucleotide (TPN), which substances join the general metabolism to cellular energy. It is reported that niacin is involved in 35 important, separate metabolic steps. The above line of reasoning inevitably leads one to consider the probability that effects in or on enzyme systems will probably be found as the basis of the mushroom observations.

Besides the dosage being important in these various substances as to the effects produced from individual to individual, must we not also take into consideration the various possible pathways of such a substance as niacin which each human may have inherited or which exist in us as potentials to assert themselves under differing metabolic conditions? Is this a part of what is meant by the biochemical individual differences that are encountered in this class of research which involves nervous system and metabolism. My work with L-tryptophan has shown that many adjustments of nervous system functioning can be secured through its correct manipulation. I believe that somewhere in its metabolism there exists close relationships to the effects observed with whole mushrooms or isolated compounds secured from them. With specific reference to mushrooms, probably several chemical compounds, working alone or in combination, will be found to be psychoneurophysiologically effective in each significant mushroom, and not only those related to tryptophan as I have been suggesting. Useful explanations will be uncovered for such unusual phenomena which have been alleged or reported, and which I believe have occurred in situations where so-called "sacred" mushroom material has been ingested, such as extra-sensory perception, psi-activity and hallucinosis. To me, it is understandable how unsophisticated or primitive people came to label this material "sacred".

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In closing, I should like to prognosticate that conceivably man's total maturity of neural functioning, including his mood, motivation, energy, even quality of thought, and some currently unsolved medical conditions, eventually may be significantly determined by manipulating combinations of food, and/or of its ingredients, and/or of other biological vegetations which are in the process of being explored. The term, psycho-dietetics, used recently at a nutrition symposium seems very apt. In that context, the quality and quantity of what one would write in a paper to be presented to a society might even depend considerably on whether he was ingesting candy-bars, pretzels, L-tryptophan or mushrooms while writing.

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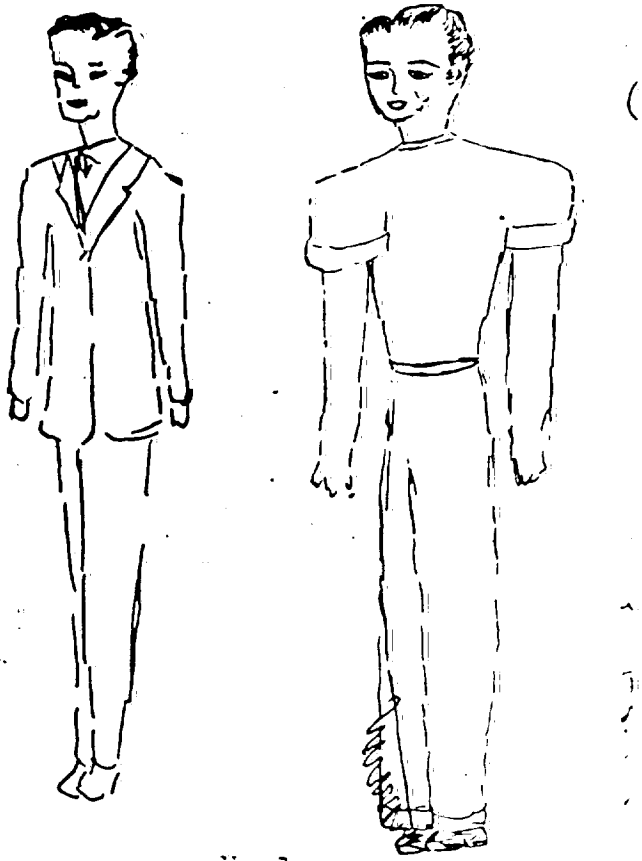
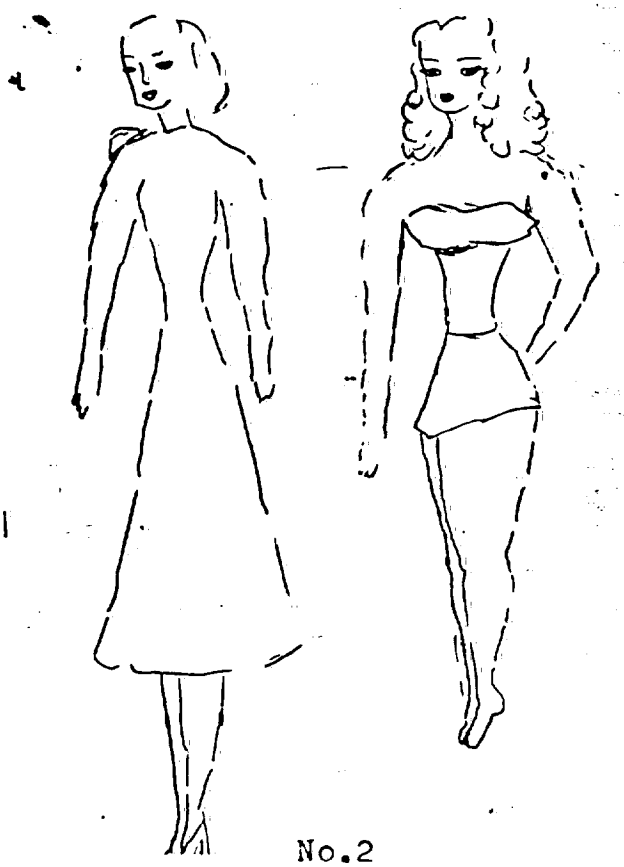
SLIDES



No.1



No.2

Draw-A-Person	Draw-A-Person	Draw-A-Person	Draw-A-Person
April 16, 1958 (before treatment)	June 3, 1958 (after treatment)	April 16, 1958 (before treatment)	June 3, 1958 (after treatment)

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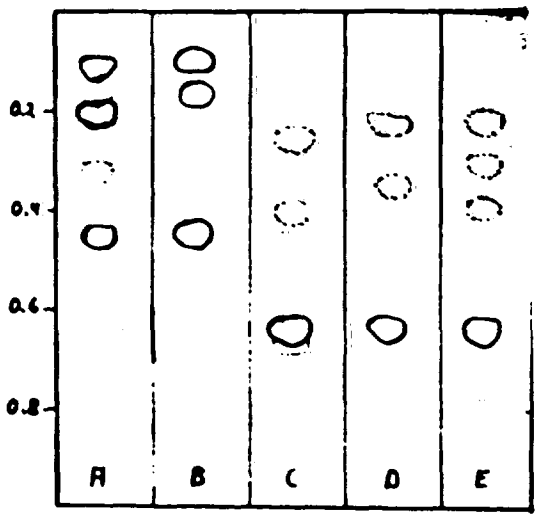
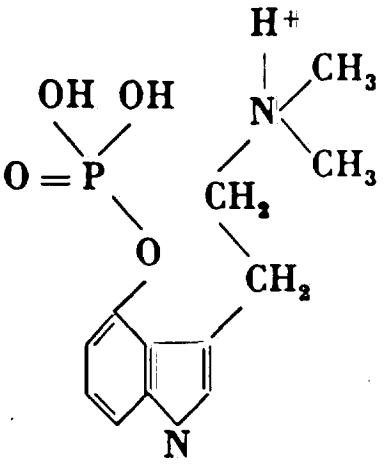


Fig. 1
Paper Chromatograms of

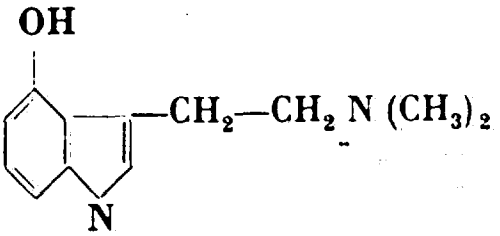
A, P. venenosus
B, P. sphrinctrinus
C, Psil. mexicana
D, Psil. cubensis
E, Psil. caerulescens

Solvent: Isopropanol - water 9:1
Detecting reagent: Ehrlich's reagent.

No.3



Psilocybin



4-Hydroxytryptamine

No.4

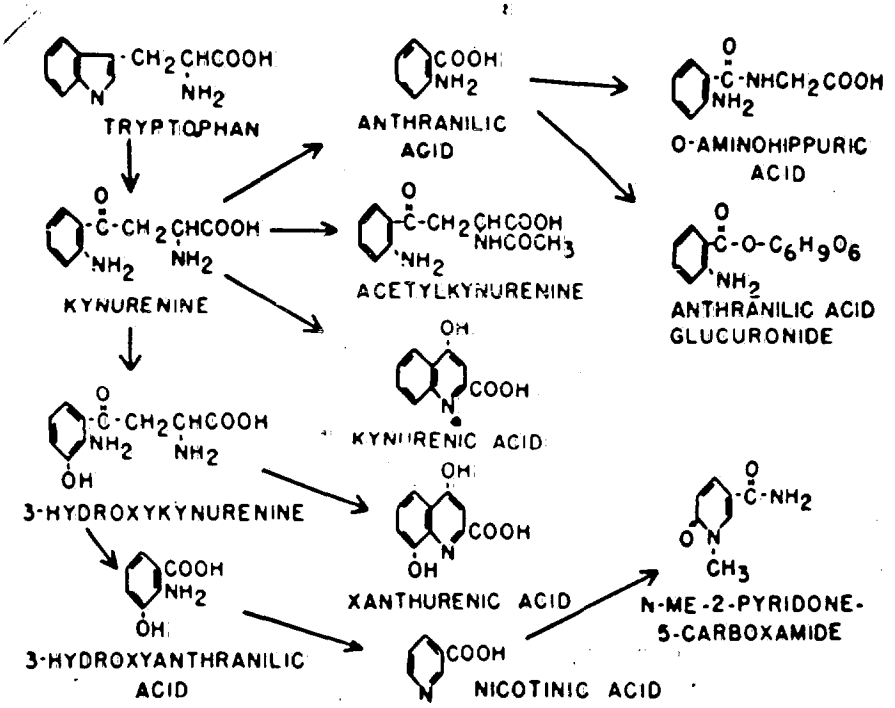


Fig. 1.—Abbreviated diagram of the pathway from tryptophan to niacin and its chief metabolite, N-methyl-2-pyridone-5-carboxamide, showing the interrelationships of the various metabolites. This figure has been published previously.[40,41]

No.5

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